



(19) Europäisches Patentamt  
European Patent Office  
Office européen des brevets



(11) Publication number: 0 411 925 A3

(12)

## EUROPEAN PATENT APPLICATION

(21) Application number: 90308469.7

(61) Int. Cl. 5: C08H 1/06

(22) Date of filing: 01.08.90

(30) Priority: 02.08.89 US 388003  
30.07.90 US 557639

(43) Date of publication of application:  
06.02.91 Bulletin 91/06

(84) Designated Contracting States:  
CH DE ES FR GB IT LI

(86) Date of deferred publication of the search report:  
14.08.91 Bulletin 91/33

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(54) Process for cross-linking collagenous materials and resulting product.

(57) The present invention relates to a process for cross-linking a proteinaceous material. The process comprises:  
i) soaking the material to be cross-linked in an aqueous solution of high osmolality; ii) incubating the material in an aqueous buffer including an amount of a photooxidative catalyst sufficient to catalyze photooxidation of the material; and iii) irradiating the material and the catalyst of step (i) with light that includes a range of wavelengths selectively absorbed by the catalyst. Irradiation is effected under conditions such that cross-linking of the material occurs. In a further embodiment, the present invention relates to a cross-linked product produced by the above-described method.

A3  
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0 411 925 A3



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EUROPEAN SEARCH  
REPORT

Application Number

EP 90 30 8469

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
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The present search report has been drawn up for all claims			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
Place of search	Date of completion of search	Examiner	
The Hague	23 May 91	LESEN H.W.M.	
CATEGORY OF CITED DOCUMENTS			
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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>7</sup> :	A1	(11) International Publication Number:	<b>WO 00/15274</b>
A61L 27/36, 27/26		(43) International Publication Date:	23 March 2000 (23.03.00)

(21) International Application Number: PCT/GB99/03013

(22) International Filing Date: 10 September 1999 (10.09.99)

(30) Priority Data:  
9819882.3 11 September 1998 (11.09.98) GB(71) Applicant (*for all designated States except US*): TISSUE SCIENCE LABORATORIES LIMITED [GB/GB]; Greyholme House, 49 Victoria Road, Aldershot, Hampshire GU11 1SJ (GB).

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(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

## Published

With international search report.

(54) Title: COLLAGENOUS TISSUE COMPOSITIONS

## (57) Abstract

Implant compositions are disclosed consisting of a biocompatible carrier medium such as a saline or dextran solution and particles of collagenous material dispersed therein. The collagenous material is derived from tissue which has been milled to provide fragments of collagen fibres which preserve the architecture of the original fibres and their molecular structure. The collagenous material is also substantially free of non-fibrous tissue proteins, glycoproteins, cellular elements and lipids or lipid residues, and is non-cytotoxic. By suitable choice of particle size and concentration, the composition may be presented in injectable form or as a paste. The compositions are suitable for application in cosmetic and reconstruction surgery.

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COLLAGENOUS TISSUE COMPOSITIONS

This invention relates to collagenous tissue compositions.

5

In recent years, much attention has been given to the development of compositions and preparations for wound treatment and for use in general and plastic surgery, in particular for the improved restoration of surgically 10 induced wounds or for the correction of physiological malfunction as, for example, of the urethral sphincter in cases of urinary incontinence.

Much attention has been focussed on the provision of 15 materials based on collagen, either of human or animal origin. In particular, considerable attention has been directed to developing preparations and materials based on animal tissues which are treated to provide compatibility, i.e. to avoid rejection of the tissues 20 when used on humans.

Earlier work by the inventors of the present application is reflected in United States Patent Specification 5397353 and EP-A-182842 which disclose methods of

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preparing collagenous materials, preferably in sheet form, and which are suitable for transplantation. The treatment is designed to produce a collagenous material which is non-antigenic so that it is not rejected and  
5 which is non-resorbable so that it forms a permanent transplant. In particular, the material described in these specifications retains the natural structure and original architecture of the natural tissue; the molecular ultrastructure of the collagen is retained.  
10 These materials have proved highly satisfactory in practice and, in particular, have shown themselves to be capable of being re-vascularised once implanted while, at the same time, being resistant to calcification. They are particularly useful in ear, nose and throat,  
15 orthopaedic, gynaecological and urological procedures and a range of hernia repairs including parastomal incisional and inguinal hernias.

The compositions described in United States Patent  
20 Specification 5397353, however, are disclosed as large scale structures, for example 0.75 mm thick and usually presented as sheets varying in size from 25 cm<sup>2</sup> to 50 cm<sup>2</sup>. This is useful for specific implant use, e.g. during restorative surgery, but is not always suited for  
25 use generally to build up soft tissues.

In cosmetic and reconstructive surgery, e.g. for the repair of small acne scars and for elevating and smoothing wrinkles, it is often desirable to use  
30 material in another form for tissue implantation or so-called augmentation which can be injected or otherwise introduced into the desired site.

Various so-called injectable implant materials have been  
35 developed for such purposes. United States Patent Specifications 5523291, 5676698 and 5705488 disclose

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injectable implant compositions for soft tissue augmentation comprising elastin and collagen and a biocompatible carrier, or flexible pouches containing such a material. The difficulty with such materials as  
5 are disclosed in these United States specifications, however, is that there is a tendency to resorption and this can mean that the implant is effective only for a limited time. Additionally, such materials do not encourage vascularisation, i.e. they do not integrate  
10 well into the surrounding healthy tissue following implantation.

Furthermore, in wound surgery, e.g. for repairing bullet wounds or injuries caused by machinery or vehicle  
15 accidents and indeed following incisional injury, there is often a problem in that tissue is lost from the wound area. This leads to the development of scars, which may be hyperplastic and disfiguring and lead to impaired body function.

20 Scars arise from the biological response of adult connective tissue to injury. Unlike foetal tissues which respond to incision or injury by regenerating new dermis to replace the lost/damaged tissue (i.e. bridging  
25 the defect with dermal collagen fibres with normal dermal collagen architecture) after birth, equivalent wounds are repaired rather than regenerated and the wound becomes filled with scar tissue. Thus the bridging tissue after birth does not replicate the  
30 original normal dermal architecture. During the repair process, fibroblasts (the cells which permeate all connective tissues and which synthesise the extra-cellular matrix including structural collagen) and small blood vessels migrate into the wound space to form  
35 highly cellular granulation tissue which transforms into the dense irregularly organised collagen mass described

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as scar tissue.

One solution to this particular tissue loss problem has been to apply three-dimensional collagen gels within the lost tissue area of the wound which subsequently acts as a matrix network for the growth of so-called histiotypic skin. The collagen used to form this particular gel is completely water-soluble and when it is applied, it is invaded with fibroblasts and small blood vessels, water is extruded and a fragile gel is formed in which the collagen molecule is polymerised to form collagen fibrils. Although reasonably successful in rebuilding the lost tissue in the area around the original wound, the initial three-dimensional matrix formed from the collagen gel does not replicate the normal matrix architecture of the body's natural tissue and, as such, the gel has no inherent stability. This inherent instability leads to the gel being rapidly re-absorbed by the body and replaced with scar-like tissue.

20

Other recent proposals to overcome the problem of scar tissue formation have involved the extremely difficult (and very expensive) use of monoclonal antibodies to suppress the action of growth factors such as transforming growth factor (TGF -  $\beta$ ).

We have now surprisingly found that the favourable properties, including resistance to resorption, resistance to calcification, granulation and the ability to become recellularized and revascularised, which characterise the large scale structures disclosed in Specification 5397353, are capable of being retained if the collagen material is presented in mouldable form at the fibre fragment level of organisation, where it can be used as a wound filler, or in injectable form for use in cosmetic and reconstructive surgery.

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According broadly to the present invention there is provided an implant composition which comprises a biocompatible carrier medium having dispersed therein particles of collagenous material, where the particles 5 comprise fragments of collagenous fibres and are thus sufficiently large to preserve the original architecture and molecular structure of the natural tissue material from which they are derived, and wherein the collagenous material is substantially free of non-fibrous tissue 10 proteins, glycoproteins, cellular elements and lipids or lipid residues, and which is non-cytotoxic. Preferably, the material is free or substantially free of antigenic polysaccharides and mucopolysaccharides. The biocompatible medium may be, for example, a saline or 15 dextran or hyaluronic acid solution.

Such compositions may vary widely in consistency. For example, if the particle size and concentration in the biocompatible medium is such as to produce a fairly 20 liquid suspension, this can be injectable provided the particles are not too large. More concentrated thicker consistency compositions may be used as pasty wound filling compositions.

25 Such materials may be prepared from collagenous materials of human or animal origin, the preferred starting material being pig dermis, by methods as disclosed in Specification 5397353 or analogously thereto. Depending on the starting material, the 30 composition may contain a proportion of elastin. It is then possible, provided care is taken, to reduce the material from large pieces to small particles which can then be formulated into a sterile injectable composition or a sterile wound filling paste.

35

In order to produce a collagen paste with appropriate

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density and rheological properties (flow rate and an ability to retain shape after moulding), a suspension of collagenous particles in a suitable carrier can be prepared to form a controllable concentration of the 5 composition.

Care must however be taken to ensure that the size reduction of the starting material is not accompanied by degradation of the molecular structure of the original 10 material. The preferred method of providing particles of an appropriate size is by grinding or milling and this is preferably carried out in a ball or hammer mill which may be cooled to an appropriate temperature. Milling may be carried out in dry form (less than 10% 15 moisture content) or in frozen hydrated form (20 - 80% moisture content).

Collagen which has been milled in a frozen hydrated state may be dehydrated by acetone extraction, freeze 20 drying or in a current of air. The dry collagen powder may be suspended in an essentially non-aqueous, non-toxic, bio-compatible medium, such as for example, glycerol prior to injection.

25 An anaesthetic as for example, lignocaine may be incorporated into the composition.

The collagenous material may be, if desired, 30 crosslinked, e.g. using a diisocyanate, in order to make it resistant to collagenolytic enzymes and thus render it substantially non-resorbable.

The preferred method of rendering the compositions 35 sterile is by gamma irradiation.

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The preferred particle size of the particles of collagenous material in the injectable compositions according to the present invention is from 50 to 500 microns. The particle size distribution may vary but 5 preferably at least 50% of the particles are within  $\pm$  35% of the average particle size. The concentration of solids in the injectable composition is preferably in the range of 10 to 70% (w/v). In contrast, in the pasty wound filling compositions, the concentration of solids 10 is generally up to 80%.

The efficacy of the compositions of the invention can be seen in vitro. It has been observed that when dispersed collagen fibre fragments (milled collagen) are seeded 15 with human or rodent fibroblasts in tissue culture, the fibroblasts attach to the collagen fragments and aggregate them to form dense tissue like discs which are easily manipulable.

20 Furthermore, when injected in vivo, milled collagen is rapidly invaded by fibroblasts and small blood vessels (much more rapidly than collagen sheets) to form a new tissue in which the collagen fibre fragments are organised into intermeshing collagen fibres similar to 25 normal dermal collagen architecture, i.e. are not resorbed and do not form scar tissue.

The injectable compositions can be used in a variety of clinical situations. For example, to control urinary 30 incontinence and more specifically in intrinsic sphincter deficiency, by peri-urethral injection to reduce lumen aperture. Cosmetic applications include the use of injection of collagenous suspensions following eyebrow uplift, for lip augmentation and to 35 rectify facial defects, frown lines and acne scars. As another example, in arthritic joints, there is often a

marked loss and damage of the smooth cartilage layer which consists of chondrocytes supported by a fibrous collagen matrix. There is evidence that under the inflammatory conditions in arthritic joints that 5 collagenase is produced which destroys the collagen matrix of the cartilage layer. If a collagenous suspension according to the invention is injected into the joint, it may assist in producing a collagenase resistant matrix to support chondrocytes and so repair 10 the damage.

An alternative clinical scenario is where it is necessary to treat a large area of skin, for example, the back of the hand or neck in elderly patients where 15 the skin has become very thin. A multi-point injection system may be employed for this purpose. Such a system may combine a number of needles mounted in a hollow block of metal or plastics material, the inlet of which is fed with collagenous suspension with a syringe, 20 metering pump, piston peristaltic pump or any other suitable device.

The collagenous compositions of the invention may also be used for the purpose of suppressing scar formation in 25 surgical wounds, the milled collagenous material again serving to introduce fibre-structured fragments into the wound space immediately during or after closing the wound by suture or tape. Although totally against convention, such a procedure has been shown to be 30 extremely beneficial. The introduction of the collagenous material fragments into newly-formed wounds, e.g. incisional spaces, provides an anatomically "thin" matrix of collagen-rich sites for the fibroblasts and small blood vessels to migrate in to from the wound 35 edges. This has a profound influence on the behaviour of the fibroblasts as within such a collagen-rich

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environment within the wound space, they do not receive the signals to produce granulation tissue and synthesise excess new collagen. In other words scar formation is largely suppressed. This simple "mechanical" approach  
5 differs from the prior art, in particular the use of monoclonal antibodies as it is far simpler to apply and far cheaper.

- 10 Use of milled collagen by injection through fine needles is somewhat limited because of the mode of introduction of collagenous material to the site where it is needed. However, the thicker consistency compositions, which allow the use of a wider spectrum of collagenous
  - 15 material fragment sizes, can be used in a variety of situations where an injectable material would not be suitable. Thus in the treatment of more extensive or severe wounds, in order to replace lost tissue and to greatly reduce the formation of scar tissue, collagen
  - 20 fibre fragments may be introduced as a pasty composition into the wound space before applying an appropriate dressing or closure by suture or tape. For example, the composition may be used for immediate reconstruction following breast lumpectomy. For skin-loss defects,
  - 25 including those following traumatic chemical or burn injury, or those presented by leg ulcers, the pasty composition may be used to replace lost dermis with appropriate cover and dressing.
- 30 The following examples will serve to illustrate the invention:

Example 1

- 35 Under sterile conditions, samples of porcine dermal collagen were cut into small pieces (1 to 3 mm<sup>3</sup>) and

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dehydrated using several changes of 100% ethanol and anhydrous acetone. Using a ball mill, the dried collagen pieces were ground and sieved to produce a fine white powder. The sieved powdered collagen was  
5 rehydrated in sterile phosphate buffered saline to produce a collagen suspension concentration of 60 to 70% (w/v).

Example 2

10 Small pieces of blotted porcine collagen were frozen in liquid nitrogen and ground in a cryogenic mill. The ground collagen fragments were suspended in sterile phosphate buffered saline to produce a collagen  
15 suspension concentration of 60 to 70% (w/v).

Example 3

To directly examine cell/collagen biointeraction, sieved  
20 powdered porcine dermal collagen was rehydrated in complete mammalian cell culture medium to produce a collagen suspension concentration of 70% (w/v) and seeded with either primary human foreskin fibroblasts or primary rat skin dermal fibroblasts.  
25 Collagen/fibroblast samples were aliquoted into costar wells and incubated at 37°C, 5 to 7% (w/v) CO<sub>2</sub> saturated humidity. As studied over a 21 day incubation period, both human and rat fibroblasts proliferated and migrated into and adhered to the porcine collagen fragments which  
30 they assembled into densely packed clumps or discs.

Example 4

To examine in vivo performance collagen suspensions were  
35 injected (0.2 ml/injection) through a 21 gauge needle intracutaneously into dorsal sites in isogenic PVG/Ola

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rats. Sequential biopsies up to 12 month post injection showed the persisting macroscopic presence of injected collagen as subdermally located white discs with no overt signs of loss of injected collagen mass nor of 5 adverse host reactions. Early biopsies showed that the injected collagen remains in situ and within 9 days is fully invaded with fibroblasts and small blood vessels. Subsequent histology showed that the collagen fibre fragments are organised into intermeshing collagen 10 fibres to produce a tissue with an architecture resembling normal dermal collagen.

Example 5

15 Under sterile conditions, samples of porcine dermal collagen produced in accordance with the process described in US-A-5397353 were cut into small pieces (1 to 3 mm<sup>3</sup>), frozen in liquid nitrogen and ground in a cryogenic mill. The ground collagen fragments were 20 suspended in sterile phosphate buffered saline to produce a pasty composition with a solids content of 80%w/v.

Example 6

25 Pockets were made in the skin of the pinnae of PG/Ola rats, the collagen paste composition inserted with a spatula and the wounds closed and secured with a spray dressing. Sites of collagen insertion were biopsied at 30 monthly intervals for histological examination. Over a period of 6 months, the collagen implants which persisted as raised skin bumps, became incorporated into surrounding host tissues and no adverse effects were found.

35

Example 7

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1 ml of the collagen paste was injected by "trocar" or large bore needle subdermally in the dorsum of PVG/Ola rats. This "soft tissue filler" persisted with no adverse host reactions over a period of six months.

5

Example 8

Full-thickness incisional skin wounds were made in the dorsum of PVG/Ola rats. The wounds were closed using  
10 interrupted sutures and a suspension of collagen composition was injected into the wounds until it extruded above the wound surface. Wounds were biopsied at 6, 8, 10 and 14 days for histological examination which revealed evidence of incisional healing in the  
15 absence of observable scar tissue.

Example 9

The collagen paste composition, with or without prior  
20 seeding with isogenic fibroblasts in culture, was used to fill 1 x 1cm full-thickness excised skin wounds in PVG/Ola rats and covered with a semi-permeable membrane (Opsite - REGISTERED TRADE MARK) as a primary dressing. Subsequent observation and histology revealed that the  
25 implanted collagen composition becomes covered by migrating epithelium from the wound margins within 28 days and acts as an effective and persisting dermal replacement.

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CLAIMS

1. An implant composition which comprises a biocompatible carrier medium having dispersed therein particles of collagenous material where the particles are sufficiently large to preserve the original fibre and molecular structure of the natural tissue material from which they are derived and wherein the collagenous material is substantially free of non-fibrous tissue proteins, glycoproteins, cellular elements and lipids or lipid residues and which is non-cytotoxic.
2. A composition according to Claim 1 wherein the collagenous material is free or substantially free of antigenic polysaccharides and mucopolysaccharides.
3. A composition according to Claim 1 or 2 wherein the biocompatible medium is saline, dextran solution, or glycerol or a non-toxic antigenic viscous polysaccharide.
4. A composition according to any one of Claims 1 to 3 wherein the collagenous material contains a proportion of elastin.
- 25 5. A composition according to any one of Claims 1 to 4 wherein the collagenous material is cross-linked.
6. A method according to any one of Claims 1 to 5 wherein the particle size of the particles of collagenous material is within the range of 50 to 500 microns.
- 30 7. A composition according to any one of the preceding Claims wherein the concentration of solids is 10 to 70 percent by weight and the consistency of the composition

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is such as to enable it to administered by injection.

8. A composition according to any one of the preceeding claims wherein the composition is of a pasty consistency.

9. An implant composition substantially as hereinbefore described with reference to the foregoing specific examples.

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/GB 99/03013

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 A61L27/36 A61L27/26

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 251 695 A (COLLAGEN CORP) 7 January 1988 (1988-01-07) claims; examples 1-4 ---	1-9
X	US 5 256 140 A (FALLICK HARRY) 26 October 1993 (1993-10-26) claims ---	1-9
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Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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Date of the actual completion of the international search

Date of mailing of the international search report

10 December 1999

20/12/1999

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/03013

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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**INTERNATIONAL SEARCH REPORT**

Information on patent family members

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